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Consensus Method for Rating 0.1μm Mycoplasma Reduction Filters

PDA Consensus Method for Rating 0.1μm Mycoplasma Reduction Filters Technical Report Team

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1.0 Introduction

Mycoplasmas (trivial name for organisms of the class Mollicutes) are well-known microbial contaminants found in biologic processes, particularly cell culture processes. Historical surveys of cell lines have found high rates of mycoplasma contamination in research labs and production facilities. ***(1,2)*** With their ability to establish occult contaminations, mycoplasmas can evade conventional bioburden assays, and even lead to changes in metabolism and phenotype of the cell culture.

Filters are rated based on performance and not on an absolute measure of pore size. The absence of a rigid peptidoglycan-based bacterial cell wall enable mycoplasmas to pass through sterilizing grade (0.2 µm) and mycoplasma reduction grade (0.1 µm) filters, potentially contaminating an entire production process. Because of these invasive capabilities, mycoplasma contamination has garnered special attention by regulatory agencies, resulting in expectations for testing and risk-mitigation. ***(3)***

USP <1043> provides categories that are useful for assessing material risks associated with mycoplasma contamination in raw materials. ***(4)*** Examples of contamination risks include:

- Process materials, which can provide a suitable environment for mycoplasma to remain present at high levels for at least 6 months ***(5)***
- Biological process fluids (typically containing either plant or animal-derived components), prepared with 0.2 µm filtration ***(6,7)***

The risk of contamination not only depends on the media, but also on where the material is used in the process and whether the process contains subsequent purification (i.e., inactivation or removal) steps. Therefore, pretreatment of raw materials (e.g., heat treatment or irradiation) should be considered, where appropriate.

In a biologics process, 0.1 µm filtration is often used in drug substance manufacturing as a mycoplasma contamination prevention measure. This barrier approach, with risk reduction as the goal, is prevalent in the mammalian cell culture industry. The concept is similar to bioburden reduction filtration used in protein purification processes. For upstream barrier applications, such as cell culture media filtration, process-specific mycoplasma reduction validation is generally not a regulatory expectation. However, based on a risk assessment, an end user may evaluate a process-specific reduction of mycoplasma using the mycoplasma consensus method as described in this technical report and a companion article published in the *PDA Journal of Science and Technology.* ***(8)***

For manufacturers of raw materials (e.g., serum) that wish to make a "mycoplasma-free" claim based on filtration, validation of the mycoplasma removal filtration process should be performed following the principles outlined in PDA *Technical Report No. 26 (Revised 2008): Sterilizing Filtration of Liquids.* ***(9)*** In addition, manufacturers of raw materials should also consider using the mycoplasma consensus method described in this technical report to grow the *Acholeplasma laidlawii* challenge organism for validation purposes. ***(8)***

1.1 Purpose

Filters are rated based on performance and not on an absolute measure of pore size. The guiding principles of this technical report describe a consensus filter challenge test for standardizing test parameters across laboratories. The express purpose of this technical report is to educate users and filter manufacturers about best practices for mycoplasma reduction filtration and suggest a consistent method which filter manufactures can use to for testing and rating the effectiveness of mycoplasma reduction filters. It describes the implementation of a specific filtration testing method and positive controls for establishing a manufacturer's claims of mycoplasma reduction for their filters.

1.2 Scope

For filter manufacturers, the consensus method described in this document is intended to be used for developing mycoplasma reduction claims for their products.

For filter end users, the consensus method provides assurance that the stated mycoplasma reduction capability for a given filter is derived from a standardized challenge test uniformly practiced and reported by filter manufacturers. In addition, the consensus method also provides cultivation parameters for *Acholeplasma laidlawii* as a challenge microorganism, if a risk assessment determines that process-specific evaluation is appropriate.